UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: **September 30, 2015**

SUBJECT: **Glyphosate** Qualitative Risk Assessment Based On CD-1 Mouse and Alpk:APfSD Wistar Rat Dietary Studies

PC Code: 417300
Decision No.: N/A
Petition No.: NA
Risk Assessment Type: N/A
TXR No.: 0057300
MRID Nos.: 00130406, 49631702 and 49704601

DP Barcode: NA
Registration No.: NA
Regulatory Action: NA
Case No.: N/A
CAS No.: 1071-83-6
40 CFR: N/A

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I. CONCLUSIONS

Male mice had significant trends for hemangiosarcomas, lung adenocarcinomas and malignant lymphomas. There was also a significant pair-wise comparison of the 5000 ppm dose group with the controls for malignant lymphomas in male mice.

Male rats had a significant trend, and a statistically significant pair-wise comparison of the high dose with the controls, for hepatocellular adenomas.

No compound-related tumors were observed in female mice or female rats.

II. ACTION REQUESTED

Prepare a qualitative risk assessment of the male mouse kidney, lung, hemangiosarcoma and lymphoma tumors and male rat liver tumors for Glyphosate.

IIIa. BACKGROUND: 1983 Mouse Study

Knezevich, A.; Hogan, G. (1983) A Chronic Feeding Study of Glyphosate (Roundup Technical) in Mice: Project No. 77-2061: BDN-77- 420. Final rept. (Unpublished study dated July 21, 1983; received August 17, 1983, under 524-308; prepared by Bio/dynamics, Inc., submitted by Monsanto Co., Washington, DC; CDL:251007-A; 251008; 251009; 251010; 251011; 251012; 251013; 251014. MRID 00130406. Acc. No. 251007. TXR Nos. 0004370 and 0005590)

The study design allocated groups of 50 CD-1 mice/sex/dose to dose levels of 0, 1000, 5000 and 30,000 ppm (equivalent to 0, 161, 835, 4945 mg/kg/day for males; 0, 195, 968, and 6069 mg/kg/day for females) of Glyphosate for 104 weeks.

IIIb. BACKGROUND: 1993 Mouse Study

Atkinson, C., Martin, T., Hudson, P., and Robb, D. (1993). Glyphosate: 104-week dietary carcinogenicity study in mice. Inveresk Research International, Tranent, EH3 2NE, Scotland. IRI Project No. 438618. April 7, 1993. MRID 49631702. Unpublished.

The study design allocated groups of 50 CD-1 mice/sex/dose to dose levels of 0, 100, 300 and 1000 mg/kg/day of Glyphosate for 104 weeks.

IIIc. BACKGROUND: 2009 Mouse Study

Nufarm (2009b). Glyphosate Technical: Dietary Carcinogenicity Study in the Mouse. Derbyshire, UK: Harlan Laboratories Ltd. (Cited in Greim *et al.*, 2015).

The study design allocated groups of 50 CD-1 mice/sex/dose to dose levels of 0, 500, 1500, or 5000 ppm (equivalent to 0, 85, 267 or 946 mg/kg/day) for 78 weeks.

IIId. BACKGROUND: 2001 Rat Study

Brammer, A. (2001). Glyphosate acid: two-year dietary toxicity and oncogenicity study in rats. Central Toxicology Laboratory, Cheshire, UK. Study No. PR1111. March 15, 2001. MRID 49704601. Unpublished.

The study design allocated groups of 52 Alpk:AP$_f$SD Wistar rats/sex/dose to dose levels of 0, 2000, 6000 and 20,000 ppm (equivalent to 0, 121, 361, and 1214 mg/kg/day for males; 0, 145, 437, and 1498 mg/kg/day for females) of Glyphosate for 104 weeks. Twelve additional rats/sex/dose were designated for interim sacrifice at week 52.

IVa. RESULTS/DISCUSSION: 1983 Mouse Study

Survival Analyses

According to the DER (TXR No. 0004370), "Mortality was low during the first 18 months of the study." An independent evaluation of mortality by HED was not performed.

Tumor Analyses

There were no statistically significant trends and no statistically significant pair-wise comparisons of the dosed groups with the controls for renal tubule tumors in male mice. The statistical analyses of the tumors in male mice were based upon *ad hoc* Fisher's Exact Test and the Exact Test for Trend (Table 1).

IVb. RESULTS/DISCUSSION: 1993 Mouse Study

Survival Analyses

According to the DER (TXR No. 0057296), "Treatment of male and female mice for 104 weeks did not increase mortality." An independent evaluation of mortality by HED was not performed.

Tumor Analyses

Male mice had a significant trend for hemangiosarcomas at $p < 0.01$. There were no statistically significant pair-wise comparisons of the dosed groups with the controls for tumors in male mice. The statistical analyses of the tumors in male mice were based upon *ad hoc* Fisher's Exact Test and the Exact Test for Trend (Table 2).

IVc. RESULTS/DISCUSSION: 2009 Mouse Study

Survival Analyses

No mortality information was available.

Tumor Analyses

Male mice had a significant trend for lung adenocarcinomas at $p < 0.05$. There was also a significant trend at $p < 0.01$, and a significant pair-wise comparison of the 5000 ppm dose group with the controls at $p < 0.05$, for malignant lymphomas in male

mice. The statistical analyses of the tumors in male mice were based upon *ad hoc* Fisher's Exact Test and the Exact Test for Trend (Table 3).

IVd. RESULTS/DISCUSSION: 2001 Rat Study

Survival Analyses

According to the study report (MRID No. 49704601), statistically higher survival ($p=0.02$) was observed in males at 20,000 ppm at the end of 104 weeks relative to controls, and an overall trend for improved survival was observed in treated males ($p=0.03$). An independent evaluation of mortality by HED was not performed.

Tumor Analyses

Male rats had a significant trend at $p < 0.01$, and a statistically significant pair-wise comparison of the 20,000 ppm dose groups with the controls at $p < 0.05$, for hepatocellular adenomas. The statistical analyses of the tumors in male rats were based upon *ad hoc* Fisher's Exact Test and the Exact Test for Trend (Table 4).

Table 1. Glyphosate – 1983 CD-1 Mouse Study
(MRID No. 00130406; TXR Nos. 0004370 and 0005590)

Male Renal Tubule Tumor Rates[+] and
Ad hoc Fisher's Exact Test and Exact Trend Test Results

	Dose (ppm)			
	0	1000	5000	30,000
Adenomas (%)	1/49 (2)	0/49 (0)	0/50 (0)	1/50 (2)
P =	0.4422	1.0000	1.0000	0.7576
Carcinomas (%)	0/49 (0)	0/49 (0)	1/50 (2)	2/50 (4)
P =	0.0635	1.0000	0.5051	0.2525
Combined (%)	1/49 (2)	0/49 (0)	1/50 (2)	3/50 (6)
P =	0.0648	1.0000	0.7576	0.3163

+Number of tumor bearing animals/Number of animals examined.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 2. Glyphosate – 1993 CD-1 Mouse Study (MRID No. 49631702)

Male Hemangiosarcoma Tumor Rates[+] and
Ad hoc Fisher's Exact Test and Exact Trend Test Results

	Dose (mg/kg/day)			
	0	100	300	1000
Hemangiosarcomas (%)	0/47 (0)	0/46 (0)	0/50 (0)	4/45 (9)
P =	0.00296**	1.00000	1.00000	0.05332

+Number of tumor bearing animals/Number of animals examined, excluding those that died before week 52.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 3. Glyphosate – 2009 CD-1 Mouse Study
(Nufarm 2009b; Cited in Greim *et al.*, 2015)

Male Lung and Lymphoma Tumor Rates[+] and
Ad hoc Fisher's Exact Test and Exact Trend Test Results

	Dose (ppm)			
	0	500	1500	5000
Lung Adenocarcinomas (%)	5/51 (10)	5/51 (10)	7/51 (14)	11/51 (22)
P =	0.02906*	0.62953	0.37996	0.08609
Malignant Lymphomas (%)	0/51 (0)	1/51 (2)	2/51 (4)	5/51 (10)
P =	0.00663**	0.50000	0.24752	0.02820*

+Number of tumor bearing animals/Number of animals examined.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 4. Glyphosate – 2001 Alpk:APfSD Wistar Rat Study (MRID No. 49704601)

Male Hepatocellular Tumor Rates[+] and
Ad hoc Fisher's Exact Test and Exact Trend Test Results

	Dose (ppm)			
	0	2000	6000	20,000
Adenomas (%)	0/52 (0)	2/52 (4)	0/52 (0)	5/52 (10)
P =	0.00804**	0.24757	1.00000	0.02826*

+Number of tumor bearing animals/Number of animals examined.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

References

Cox, D.R. (1972) Regression Models and Life Tables (with discussion). J. Royal Stat. Soc. Ser. B. 34, 187-220.

Gart, J.J., D. Krewski, P.N. Lee, R.E. Tarone, and J. Wahrendorf (1986) The Design and Analysis of Long-Term Animal Experiments. In: Statistical Methods in Cancer Research, Volume III. IARC Scientific Publications No. 79. Lyon, France: International Agency for Research on Cancer, p. 18.

Peto, R., M. Pike, N. Day, R. Gray, P. Lee, S. Parish, J. Peto, S. Richard, and J. Wahrendorf (1980) Guidelines for Simple, Sensitive, Significant Tests for Carcinogenic Effects in Long-Term Animal Experiments. In: Monographs on the long-term and short-term screening assays for carcinogens: a critical appraisal. IARC Monographs, Supplement 2. Lyon, France: International Agency for Research on Cancer, pp. 311-426.

Thomas, D.G., N. Breslow, and J.J. Gart (1977) Trend and Homogeneity Analyses of Proportions and Life Table Data. Computers and Biomedical Research 10, 373-381.